A Markov chain to probe chromosomal instability in tumor evolution and drug resistance

Sergi Elizalde

Dartmouth College

joint work with Sam Bakhoum, Ashley Laughney and Giulio Genovese

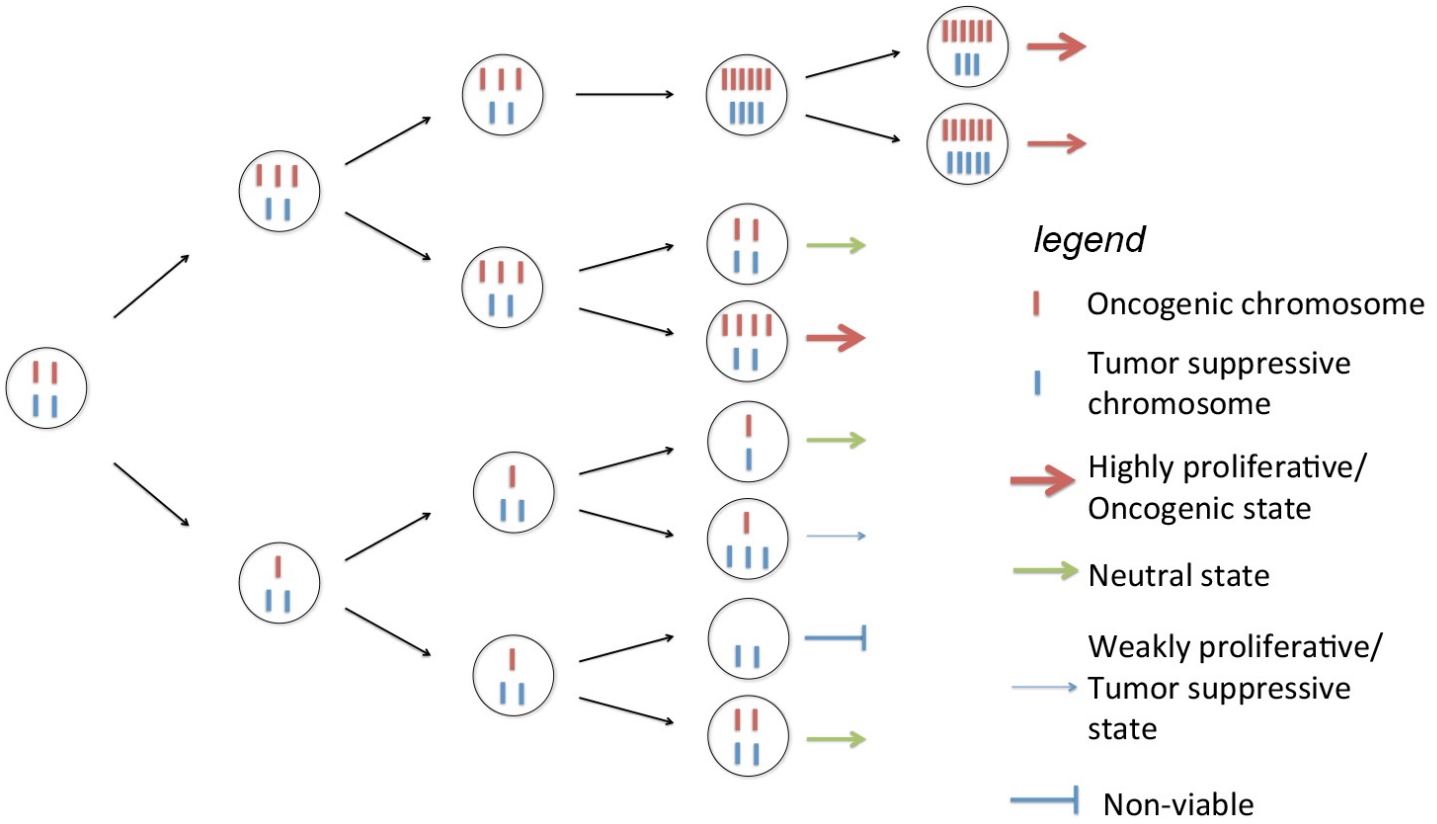
Sloan-Kettering Institute, Computational Biology Program

Science In Progress

Aug 4, 2015

Missegregation

During mitosis, cancer cells undergo chromosome missegregation events, causing one of the two daughter cells to inherit more copies of a chromosome than the other.



Advantages of genomic instability

It has been observed that

- more copies of oncogenic chromosomes (with proliferative genes) increase the cell's chances of surviving, while
- more copies of tumor supressive chromosomes (with anti-profiferative genes) increase its chances of dying.

Advantages of genomic instability

It has been observed that

- more copies of oncogenic chromosomes (with proliferative genes) increase the cell's chances of surviving, while
- more copies of tumor supressive chromosomes (with anti-profiferative genes) increase its chances of dying.

A recent genomic analysis by Davoli et al. assigned scores to individual chromosomes based on the presence of such genes.

Since the karyotype of a cell affects its fitness level, genomic instability allows for Darwinian selection to occur.

History

The first stochastic model of missegregation was developed by Gusev, Kagansky and Dooley in 2000.

Their model is quite straightforward but it has a few disadvantages:

- Simulations are very slow.
- It can't be analyzed mathematically to find long-term behavior.
- It doesn't account for chromosome scores, and its predictions are unrealistic.

History

The first stochastic model of missegregation was developed by Gusev, Kagansky and Dooley in 2000.

Their model is quite straightforward but it has a few disadvantages:

- Simulations are very slow.
- It can't be analyzed mathematically to find long-term behavior.
- It doesn't account for chromosome scores, and its predictions are unrealistic.

We will build a Markov chain model that addresses these 3 issues.

Assumptions of our model

- Each copy of a chromosome has probability p of missegregating at a given cell division, independent from other copies. Typically, $p \approx 0.0025$.

Assumptions of our model

- Each copy of a chromosome has probability p of missegregating at a given cell division, independent from other copies. Typically, $p \approx 0.0025$.
- If the number of copies of any chromosome reaches 0 or goes above N (typically $N = 8$), the cell dies.

Assumptions of our model

- Each copy of a chromosome has probability p of missegregating at a given cell division, independent from other copies. Typically, $p \approx 0.0025$.
- If the number of copies of any chromosome reaches 0 or goes above N (typically $N = 8$), the cell dies.
- Starting from a single founder cell, all the cells in the colony divide simultaneously at each generation.
- The karyotype of a cell is the vector $(n_1, n_2, \ldots, n_{23})$ where n_k is the number of copies of chromosome k. An alive cell has $1 \leq n_k \leq N$ for all k.

Simulations vs. Markov chain

We can implement this model and run a forward simulation. However, simulations are slow because we keep track of the karyotypes of all the cells.

Instead, we will build a Markov chain that describes the average distribution of karyotypes. Main advantages:

- Computations are much faster, since they amount to taking powers of matrices.
- We can analyze the Markov chain mathematically to predict long-term behavior.

Additional simplifications

- Since missegregations of different chromosomes are independent, we focus on one type of chromosome at a time.

  Our Markov chain has states $0, 1, 2, \ldots, N$, where state i corresponds to cells with i copies of the chromosome, with an absorbing state 0 corresponding to dead cells.

  The probability of a given karyoptype $(n_1, \ldots, n_{23})$ is obtained by multiplying the probability that the Markov chain corresponding to chromosome k is in state n_k for $1 \leq k \leq 23$.

Additional simplifications

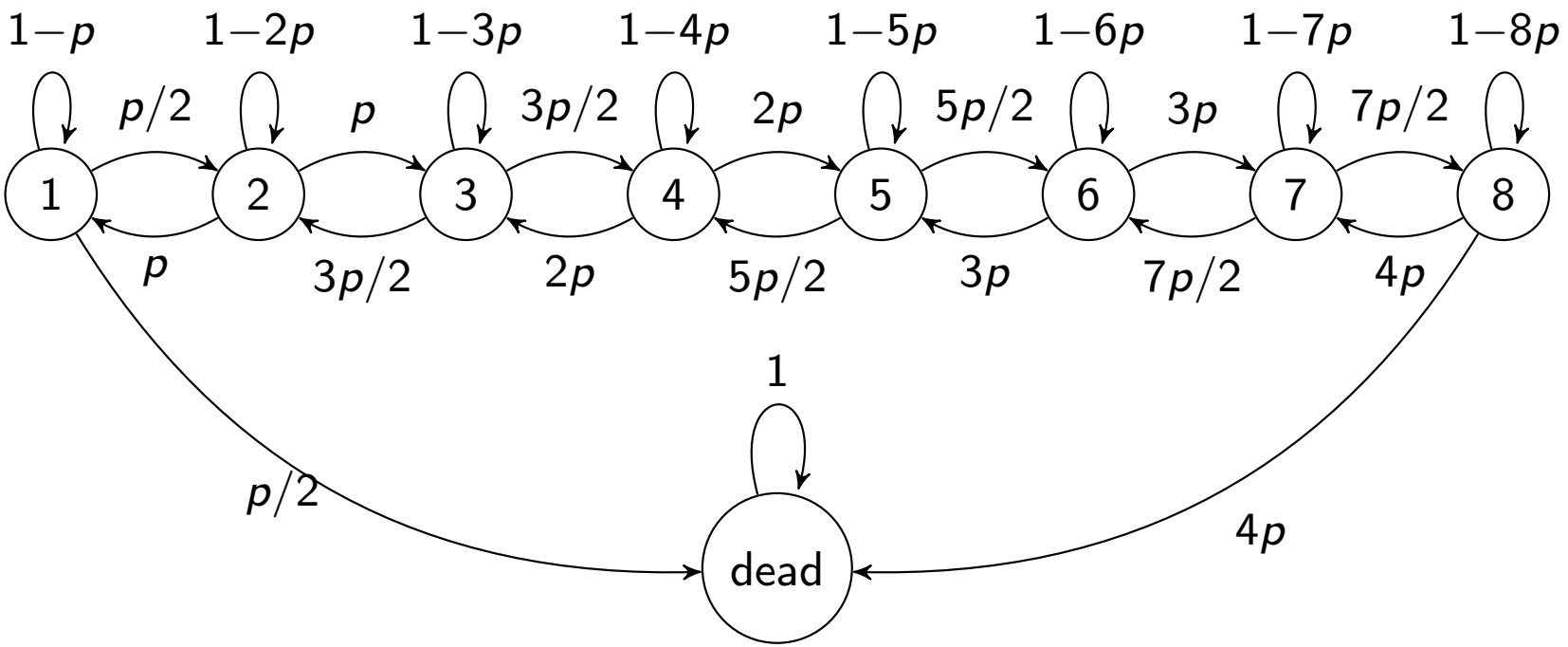
- Since missegregations of different chromosomes are independent, we focus on one type of chromosome at a time.

  Our Markov chain has states $0, 1, 2, \ldots, N$, where state i corresponds to cells with i copies of the chromosome, with an absorbing state 0 corresponding to dead cells.

  The probability of a given karyoptype $(n_1, \ldots, n_{23})$ is obtained by multiplying the probability that the Markov chain corresponding to chromosome k is in state n_k for $1 \leq k \leq 23$.

- We disregard the highly unlikely event that multiple copies of the same chromosome in a cell missegregate simultaneously.

The Markov chain for the basic model



The transition matrix

Each chromosome copy produces 0, 1 or 2 copies in a random daughter cell, with probability $p/2$, $1-p$ and $p/2$, respectively.

For a cell with i copies, the probability that a random daughter has j copies is given by the coefficient of x^j in

$$\left(\frac{p}{2}+(1-p)x+\frac{p}{2}x^2\right)^i \approx \frac{ip}{2}x^{i-1}+(1-ip)x^i+\frac{ip}{2}x^{i+1},$$

ignoring quadratic terms in p.

The transition matrix

Each chromosome copy produces 0, 1 or 2 copies in a random daughter cell, with probability $p/2$, $1-p$ and $p/2$, respectively.

For a cell with i copies, the probability that a random daughter has j copies is given by the coefficient of x^j in

$$\left(\frac{p}{2}+(1-p)x+\frac{p}{2}x^2\right)^i \approx \frac{ip}{2}x^{i-1}+(1-ip)x^i+\frac{ip}{2}x^{i+1},$$

ignoring quadratic terms in p.

This gives the transition matrix:

$$M_{ij}=\begin{cases}1-ip & \text{if } i=j,\\ ip/2 & \text{if } |i-j|=1,\\ 0 & \text{if } |i-j|\geq 2,\end{cases}$$

for $1\leq i,j\leq N$.

The transition matrix

For example, for $N = 8$, we get

$$\left[\begin{array}{c|cccccccc}
1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ \hline
p/2 & 1-p & p/2 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & p & 1-2p & p & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 3p/2 & 1-3p & 3p/2 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 2p & 1-4p & 2p & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 5p/2 & 1-5p & 5p/2 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 3p & 1-6p & 3p & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 7p/2 & 1-7p & 7p/2 \\
4p & 0 & 0 & 0 & 0 & 0 & 0 & 4p & 1-8p
\end{array}\right].$$

The transition matrix

For example, for $N = 8$, we get

$$\left[\begin{array}{c|cccccccc}
1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ \hline
p/2 & 1-p & p/2 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & p & 1-2p & p & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 3p/2 & 1-3p & 3p/2 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 2p & 1-4p & 2p & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 5p/2 & 1-5p & 5p/2 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 3p & 1-6p & 3p & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 7p/2 & 1-7p & 7p/2 \\
4p & 0 & 0 & 0 & 0 & 0 & 0 & 4p & 1-8p
\end{array}\right].$$

Let $\mathbf{M}$ be the matrix obtained by removing the row and column corresponding to the dead state.

The transition matrix

For example, for $N = 8$, we get

$$\mathbf{M} = \begin{bmatrix} 1-p & p/2 & 0 & 0 & 0 & 0 & 0 & 0 \\ p & 1-2p & p & 0 & 0 & 0 & 0 & 0 \\ 0 & 3p/2 & 1-3p & 3p/2 & 0 & 0 & 0 & 0 \\ 0 & 0 & 2p & 1-4p & 2p & 0 & 0 & 0 \\ 0 & 0 & 0 & 5p/2 & 1-5p & 5p/2 & 0 & 0 \\ 0 & 0 & 0 & 0 & 3p & 1-6p & 3p & 0 \\ 0 & 0 & 0 & 0 & 0 & 7p/2 & 1-7p & 7p/2 \\ 0 & 0 & 0 & 0 & 0 & 0 & 4p & 1-8p \end{bmatrix}.$$

Let $\mathbf{M}$ be the matrix obtained by removing the row and column corresponding to the dead state.

Properties of the transition matrix

- $(\mathbf{M}^g)_{i,j}$ is the proportion of cells that have j copies after g generations, starting with a founder cell with i copies.

Properties of the transition matrix

- $(\mathbf{M}^g)_{i,j}$ is the proportion of cells that have j copies after g generations, starting with a founder cell with i copies.
- Let $s_g(i) =$ sum of the entries of the ith row of $\mathbf{M}^g$. Then

$$2^g \prod_{k=1}^{23} s_g(n_k)$$

is the expected number of alive cells after g generations when the founder cell has n_k copies of chromosome k for each k.

Properties of the transition matrix

- $(\mathbf{M}^g)_{i,j}$ is the proportion of cells that have j copies after g generations, starting with a founder cell with i copies.
- Let $s_g(i) =$ sum of the entries of the ith row of $\mathbf{M}^g$. Then

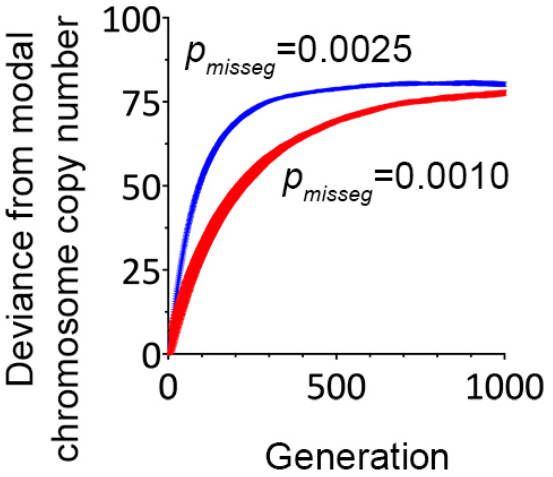
$$2^g \prod_{k=1}^{23} s_g(n_k)$$

  is the expected number of alive cells after g generations when the founder cell has n_k copies of chromosome k for each k.
- For a vector $\mathbf{v}$ describing the initial distribution of the number of copies, the vector $\mathbf{v}\mathbf{M}^g$, normalized so its entries sum to one, is the distribution among alive cells of the number of copies after g generations.

Deviance from modal chromosome copy number

Forward Matlab simulation:

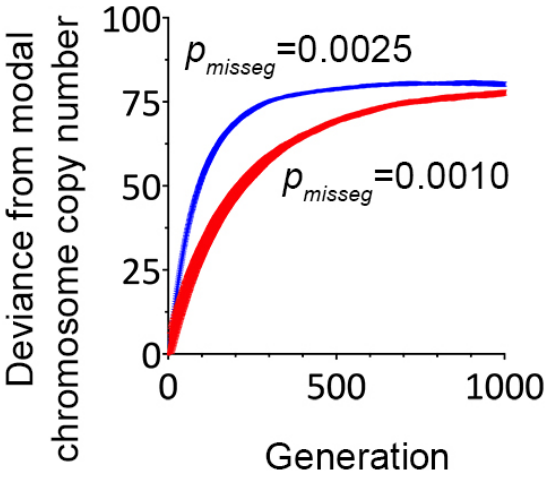
(founder cell has $n_{chrom} = 4$ copies)



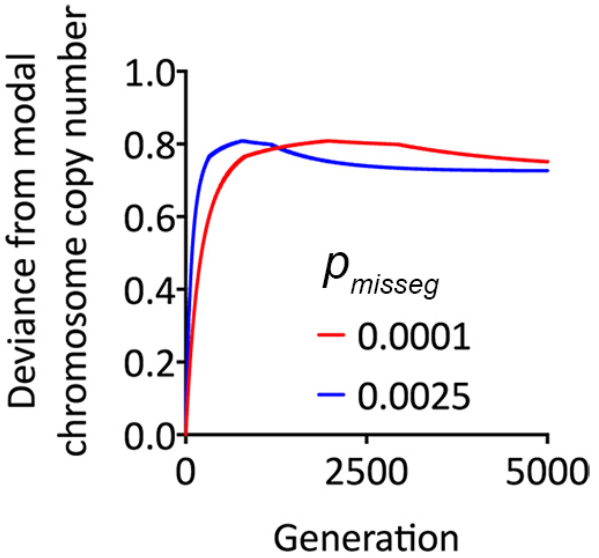
Deviance from modal chromosome copy number

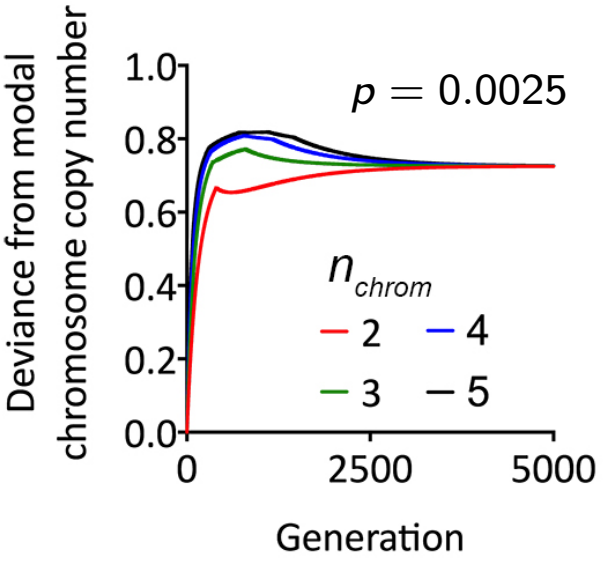
Forward Matlab simulation:

(founder cell has $n_{chrom} = 4$ copies)



Markov chain model:

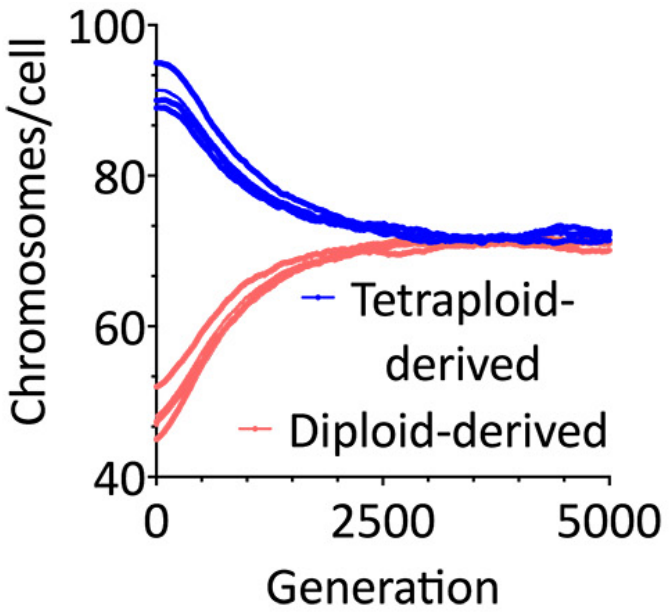




Average number of copies over time

Forward Matlab simulation:

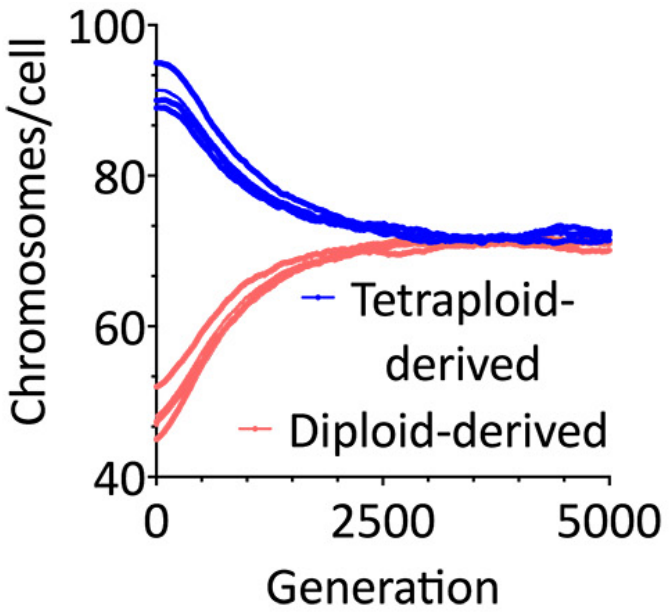
($p = 0.0025$)



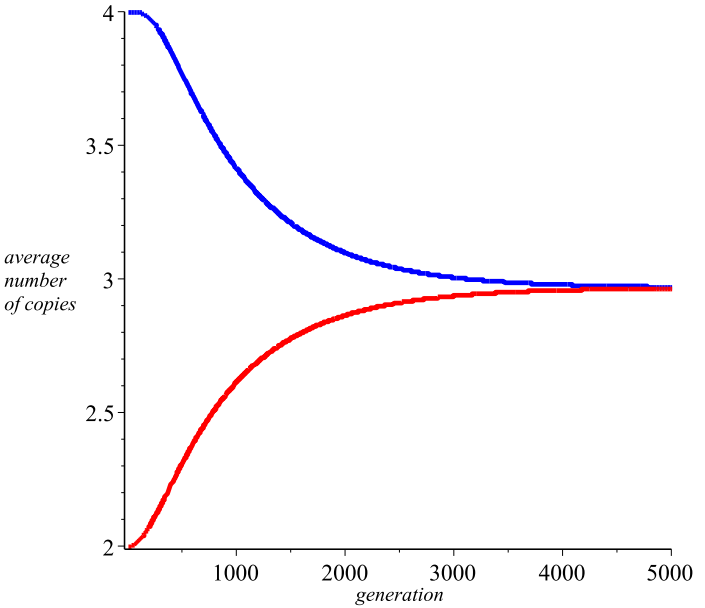
Average number of copies over time

Forward Matlab simulation:

($p = 0.0025$)



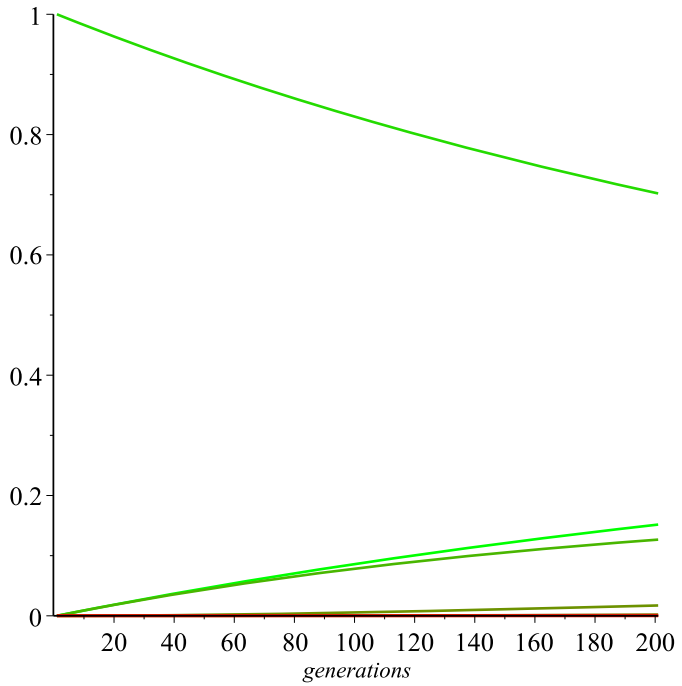
Markov chain model:



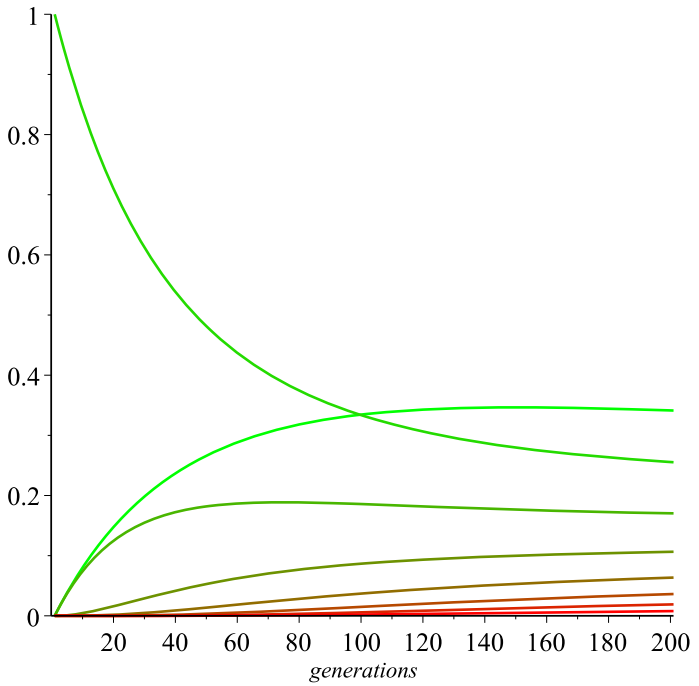
We observe convergence to a near-triploid state.

Distribution of the number of copies over time

The following figures are for the Markov chain model with $N = 8$ and a diploid founder cell. Each curve represents a number of copies: 1, 2, 3, 4, 5, 6, 7, 8.



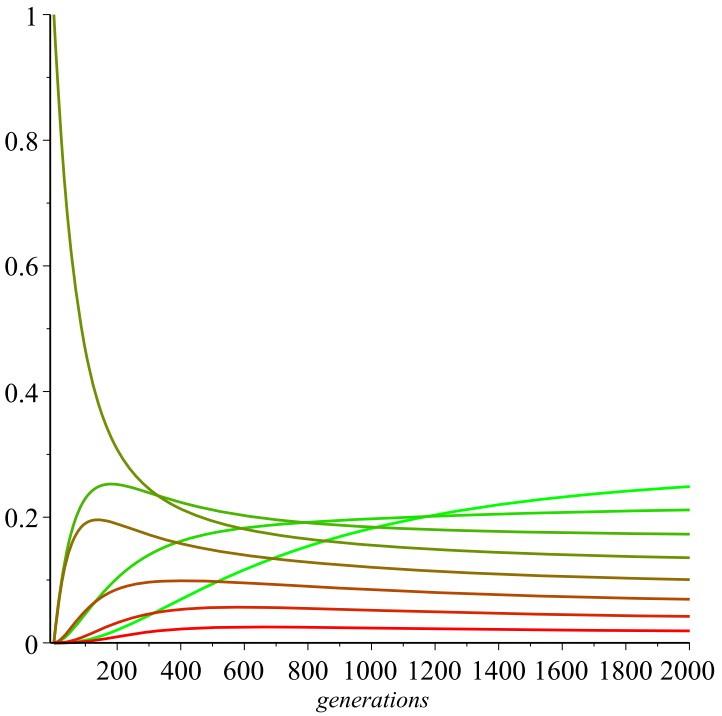
$p = 0.001$



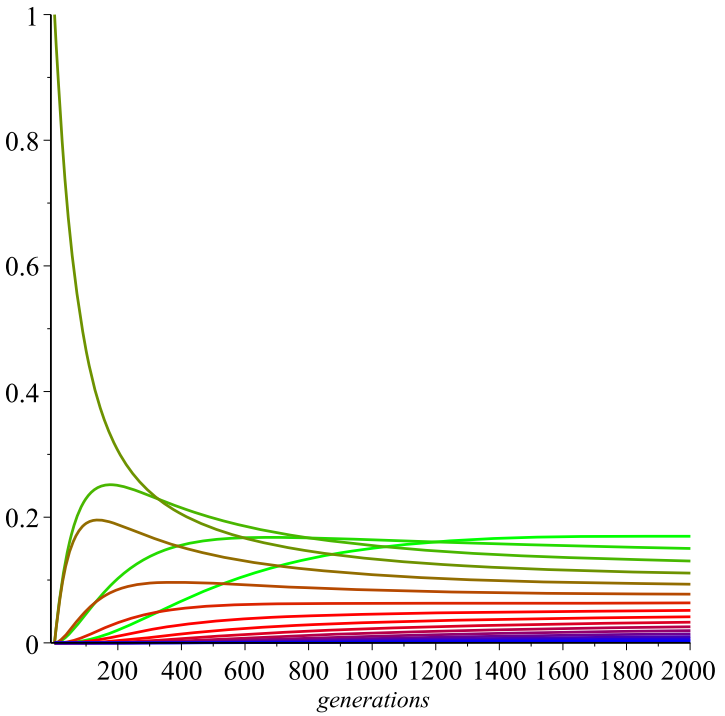
$p = 0.01$

Distribution of number of copies over time

Now take $p = 0.0025$ and run 2000 generations, with a tetraploid founder cell. Each curve represents a given number of copies:
1 , 2, 3, 4, 5, 6, 7, 8 , 9, 10, 11, 12, 13, 14, 15, 16.



$N = 8$



$N = 16$

The limiting behavior

We are interested in the limiting distribution of the number of chromosome copies (among alive cells) when the number of generations g tends to infinity.

The limiting behavior

We are interested in the limiting distribution of the number of chromosome copies (among alive cells) when the number of generations g tends to infinity.

Since our Markov chain has an absorbing state, its stationary distribution only shows that $\frac{\#\text{alive cells}}{2^g} \to 0$ as $g \to \infty$.

The limiting behavior

We are interested in the limiting distribution of the number of chromosome copies (among alive cells) when the number of generations g tends to infinity.

Since our Markov chain has an absorbing state, its stationary distribution only shows that $\frac{\#\text{alive cells}}{2^g} \to 0$ as $g \to \infty$.

However, we can use a result from probability theory to restrict to non-absorbing states (equivalently, alive cells):

Theorem

Let ρ be the largest eigenvalue of $\mathbf{M}$. The limiting distribution conditional on the non-absorbing states is given by the vector $\mathbf{v}$ satisfying $\mathbf{vM} = \rho\mathbf{v}$ and $\sum_{i=1}^{N} v_i = 1$.

The limiting behavior

In particular, this limiting distribution does not depend on the number of copies of the founder cell.

The limiting behavior

In particular, this limiting distribution does not depend on the number of copies of the founder cell.

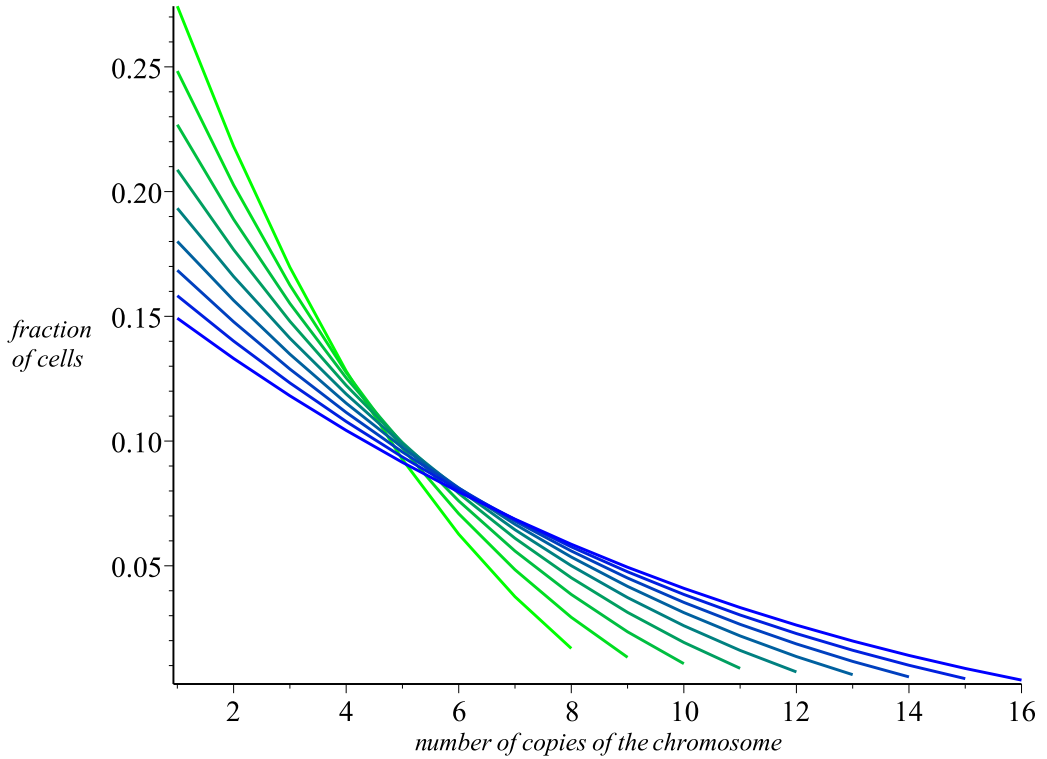
Surprisingly, we can prove that it does not depend on the missegregation rate either:

Theorem

The limiting distribution of the above basic model conditional on the non-absorbing states is independent of p.

The limiting distribution

Limiting distributions for $N = 8, 9, 10, 11, 12, 13, 14, 15, 16$.



The modal chromosomal number is always 1, but this will change once we incorporate chromosome scores.

Chromosome scores and survival probability

Following experiments by Davoli et al., we assign a score s_k to each chromosome k. The total score of a cell with karyotype $(n_1, \ldots, n_{23})$ is:

$$S = \sum_{k=1}^{23} s_k n_k,$$

Chromosome scores and survival probability

Following experiments by Davoli et al., we assign a score s_k to each chromosome k. The total score of a cell with karyotype $(n_1, \ldots, n_{23})$ is:

$$S = \sum_{k=1}^{23} s_k n_k,$$

and its survival probability at a given generation is

$$Q_{\text{surv}} = e^{c+dS}$$

for some parameters c and $d > 0$.

Chromosome scores and survival probability

Following experiments by Davoli et al., we assign a score s_k to each chromosome k. The total score of a cell with karyotype $(n_1, \ldots, n_{23})$ is:

$$S = \sum_{k=1}^{23} s_k n_k,$$

and its survival probability at a given generation is

$$Q_{\text{surv}} = e^{c+dS}$$

for some parameters c and $d > 0$.

Again, we can implement this model and run simulations.

Instead, we will incorporate the chromosome scores into the Markov chain, and use it to run fast computations and determine limiting behavior.

Decomposing the survival probability

$$Q_{\text{surv}} = e^{c+dS} = e^{c+d\,\sum_k s_k n_k} = \prod_{k=1}^{23} \underbrace{e^{c/23+d\,s_k n_k}}_{q_k(n_k)}.$$

Decomposing the survival probability

$$Q_{\text{surv}} = e^{c+dS} = e^{c+d\sum_k s_k n_k} = \prod_{k=1}^{23} \underbrace{e^{c/23+d\, s_k n_k}}_{q_k(n_k)}.$$

Let

$$q_k(i) = e^{c/23+ds_k i} = C\mu^i$$

denote the contribution to the survival probability from chromosome k, where $C = e^{c/23}$ and $\mu = e^{ds_k}$.

Decomposing the survival probability

$$Q_{\text{surv}} = e^{c+dS} = e^{c+d\sum_k s_k n_k} = \prod_{k=1}^{23} \underbrace{e^{c/23+d\, s_k n_k}}_{q_k(n_k)}.$$

Let

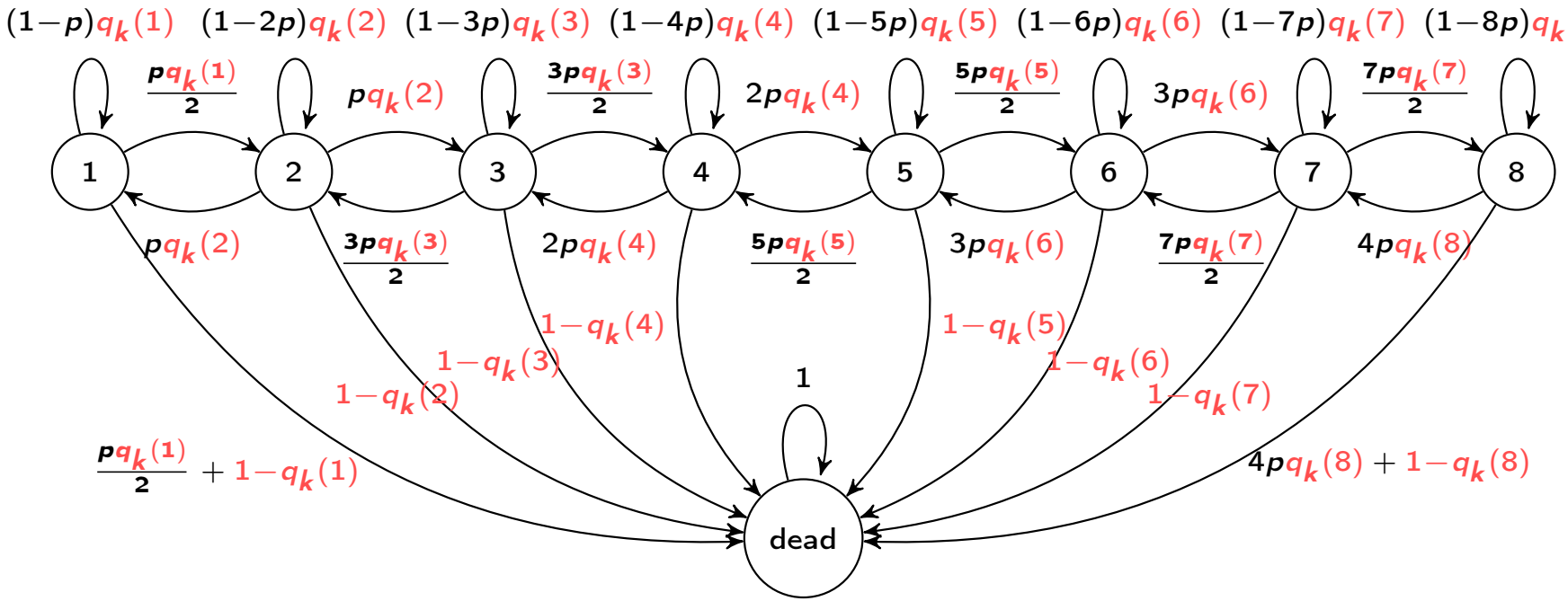
$$q_k(i) = e^{c/23+ds_k i} = C\mu^i$$

denote the contribution to the survival probability from chromosome k, where $C = e^{c/23}$ and $\mu = e^{ds_k}$.

Oncogenic $\Leftrightarrow s_k > 0 \Leftrightarrow \mu > 1$.
Tumor-suppressive $\Leftrightarrow s_k < 0 \Leftrightarrow \mu < 1$.

This equation allows us to break up the model into 23 independent Markov chains, one for each type of chromosome.

The Markov chain for chromosome k



A cell with i copies of the chromosome has probability $1-q_k(i)$ of dying, and probability $q_k(i)$ of surviving and dividing as in the basic model.

The transition matrix

The transition matrix $\mathbf{A}^{(k)}$ restricted to alive cells is:

$$A_{ij}^{(k)} = \begin{cases} (1-ip)\, q_k(i) & \text{if } i = j, \\ ip\, q_k(i)/2 & \text{if } |i-j| = 1, \\ 0 & \text{if } |i-j| \geq 2, \end{cases}$$

for $1 \leq i, j \leq N$.

The transition matrix

The transition matrix $\mathbf{A}^{(k)}$ restricted to alive cells is:

$$A_{ij}^{(k)} = \begin{cases} (1-ip)\, q_k(i) & \text{if } i = j, \\ ip\, q_k(i)/2 & \text{if } |i-j| = 1, \\ 0 & \text{if } |i-j| \geq 2, \end{cases}$$

for $1 \leq i, j \leq N$.

Letting $s_g^{(k)}(i) =$ sum of the entries of the ith row of $(\mathbf{A}^{(k)})^g$,

$$2^g \prod_{k=1}^{23} s_g^{(k)}(n_k)$$

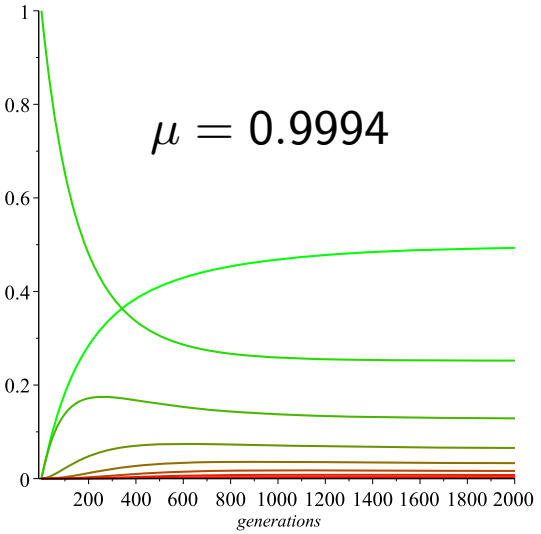
is the expected number of alive cells after g generations when the founder cell has n_k copies of chromosome k for each k.

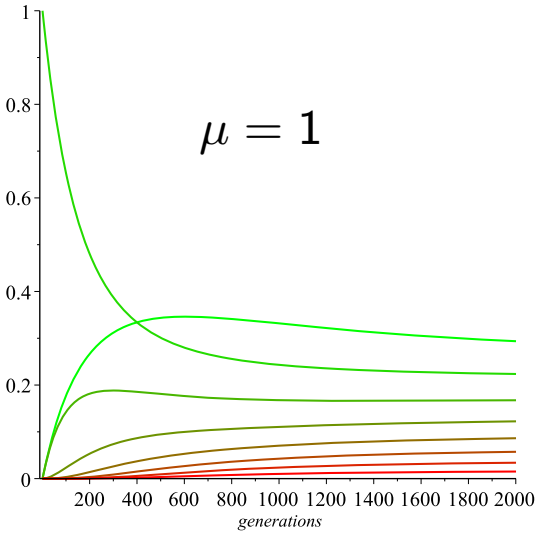
Distribution of the number of copies over time

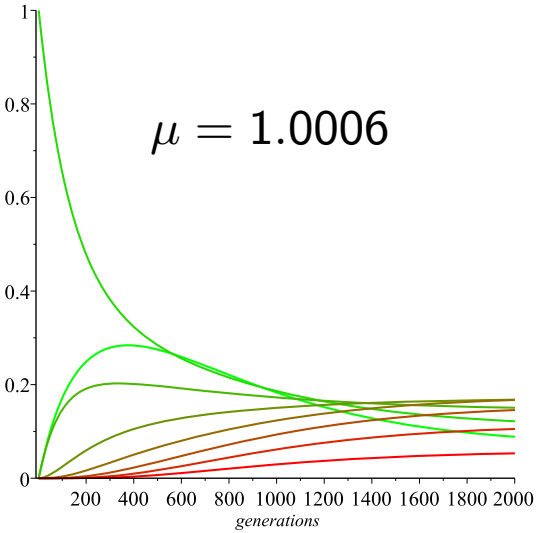
In human chromosomes, $\mu \in [0.9994, 1.0012]$.

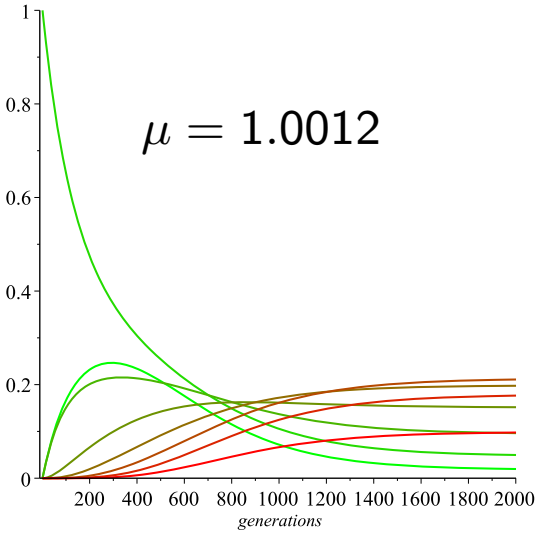
Fix $p = 0.0025$ and a founder cell with 2 copies. Run for 2000 generations.

Each curve represents a number of copies:
1, 2, 3, 4, 5, 6, 7, 8.







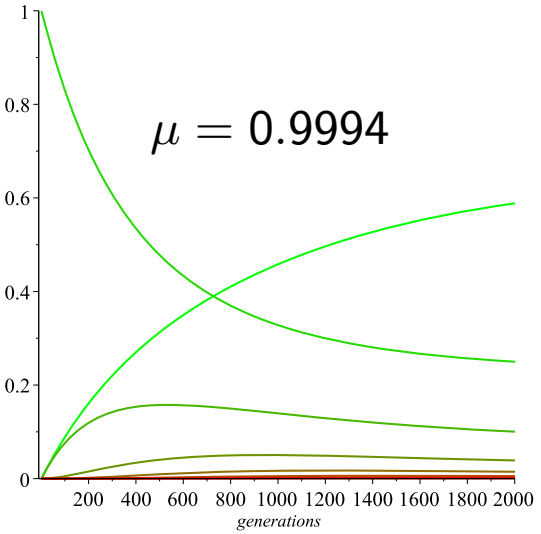


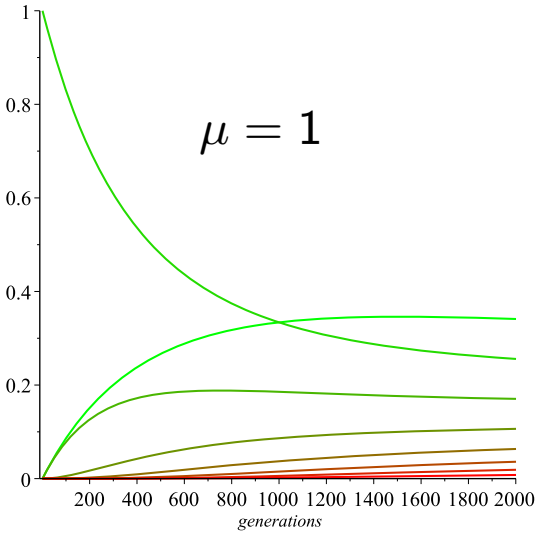
Distribution of the number of copies over time

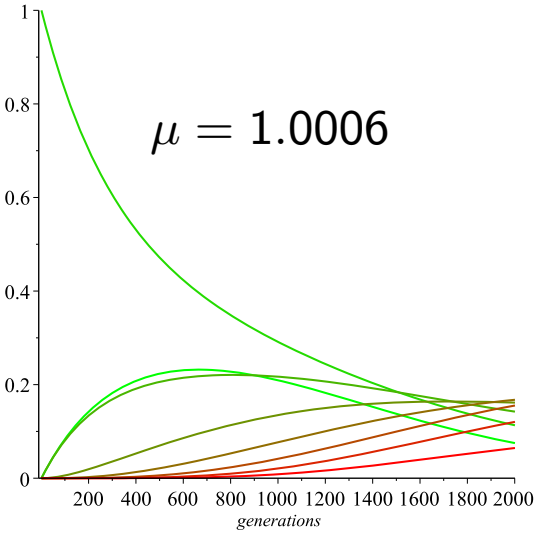
In human chromosomes, $\mu \in [0.9994, 1.0012]$.

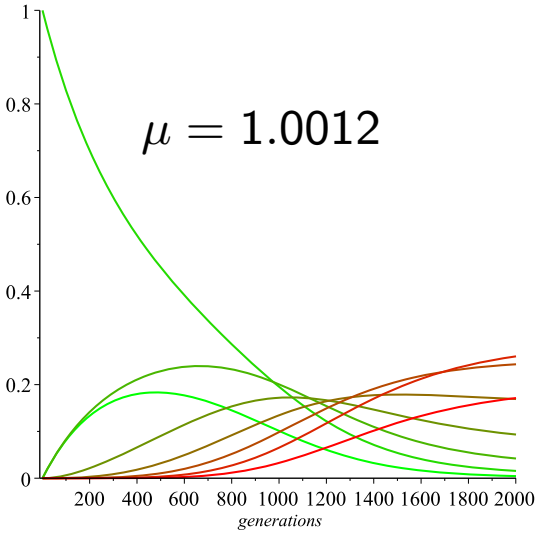
Fix $p = 0.001$ and a founder cell with 2 copies. Run for 2000 generations.

Each curve represents a number of copies:
1, 2, 3, 4, 5, 6, 7, 8.









The limiting behavior

As before, if ρ is the largest eigenvalue of $\mathbf{A}^{(k)}$, the limiting distribution conditional on the non-absorbing states is given by the vector $\mathbf{v}$ satisfying $\mathbf{v}\mathbf{A}^{(k)} = \rho\mathbf{v}$ and $\sum_{i=1}^{N} v_i = 1$.

The limiting behavior

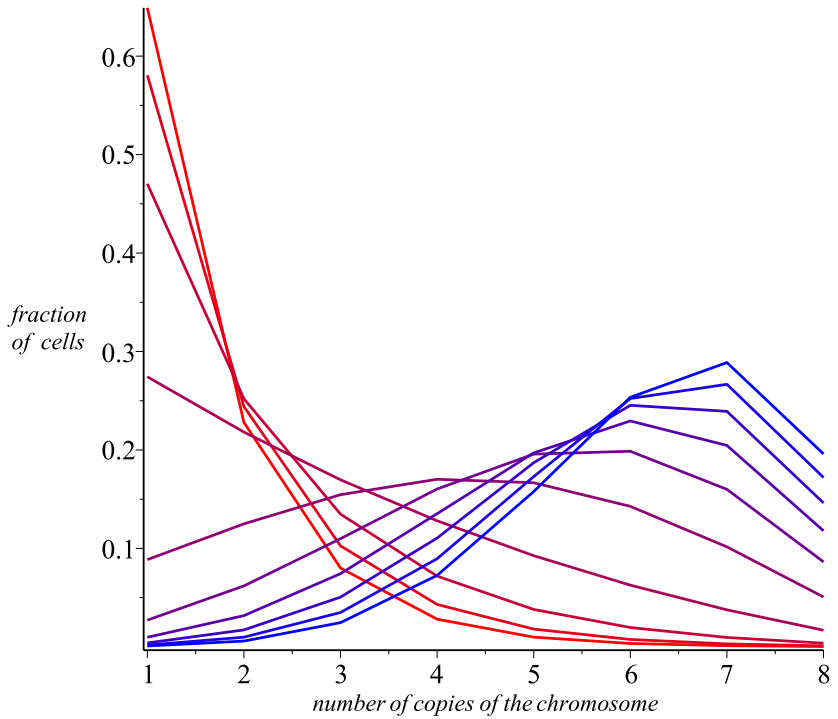
As before, if ρ is the largest eigenvalue of $\mathbf{A}^{(k)}$, the limiting distribution conditional on the non-absorbing states is given by the vector $\mathbf{v}$ satisfying $\mathbf{v}\mathbf{A}^{(k)} = \rho\mathbf{v}$ and $\sum_{i=1}^{N} v_i = 1$.

Again, this limiting distribution does not depend on the number of copies of the founder cell.

However, unlike for the model without scores, it now depends on p and on μ (equivalently, on the chromosome score).

The limiting distribution

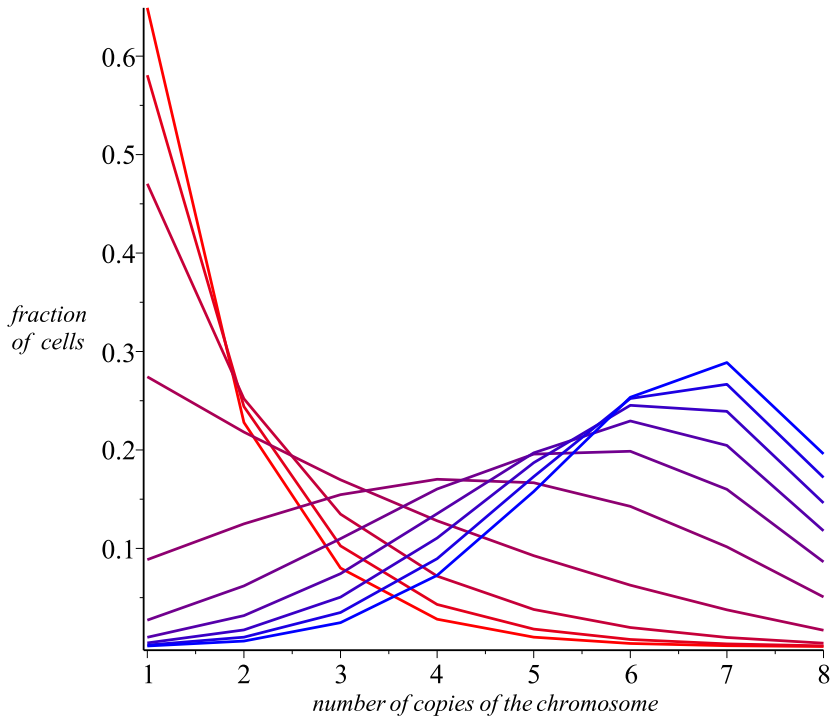
Liming distributions for $\mu = 0.9994$, 0.9996, 0.9998, 1.0000, 1.0002, 1.0004, 1.0006, 1.0008, 1.0010, 1.0012.



$p = 0.001$

The limiting distribution

Liming distributions for $\mu = 0.9994$, 0.9996, 0.9998, 1.0000, 1.0002, 1.0004, 1.0006, 1.0008, 1.0010, 1.0012.



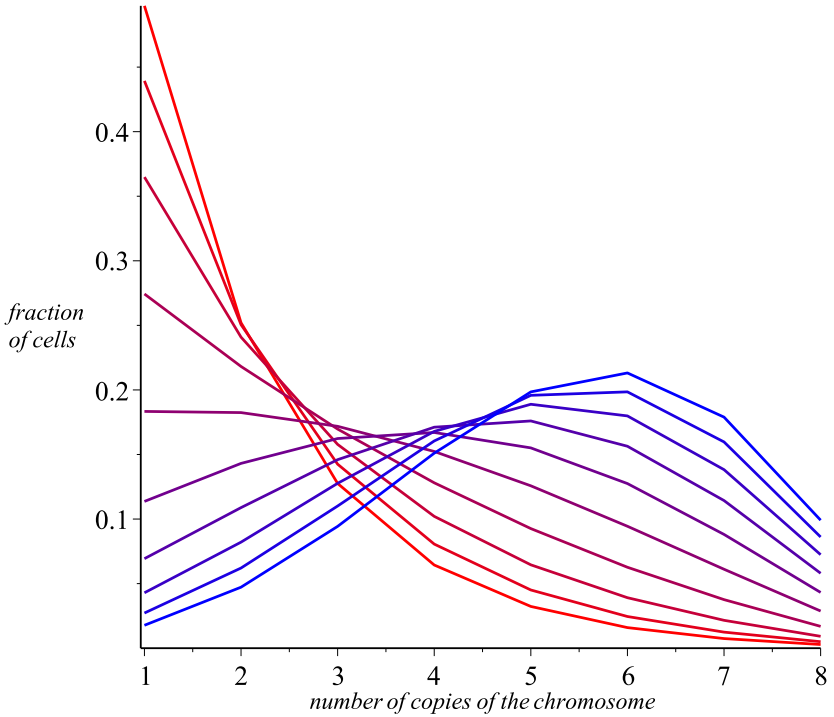
$p = 0.001$

For higher chromosome scores, the limiting distribution favors higher copy numbers.

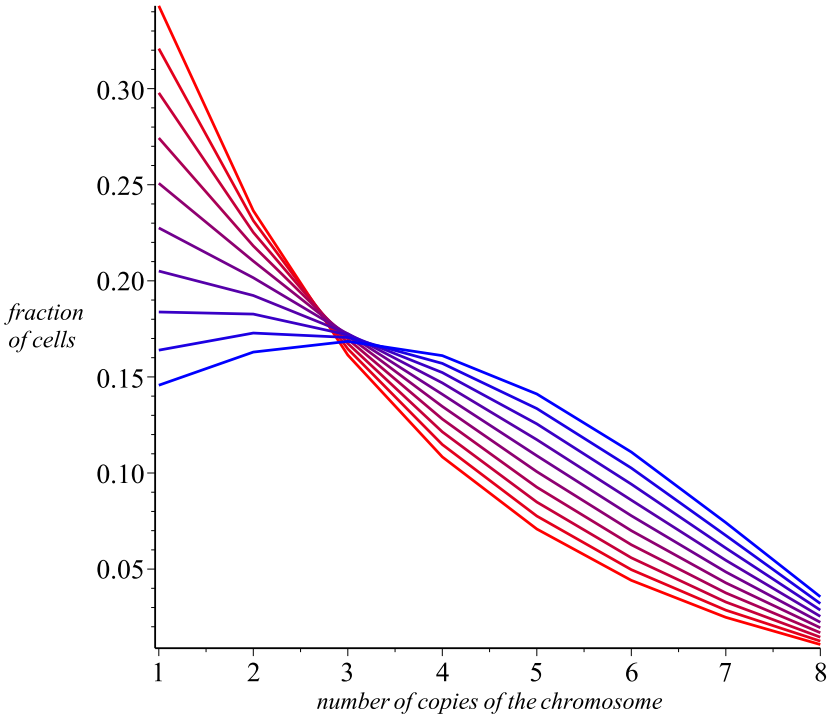
For positive chromosome scores ($\mu > 1$), the modal number of copies soon becomes higher than one, making this more realistic than the model without scores.

The limiting distribution

Liming distributions for $\mu = 0.9994$, 0.9996, 0.9998, 1.0000, 1.0002, 1.0004, 1.0006, 1.0008, 1.0010, 1.0012.



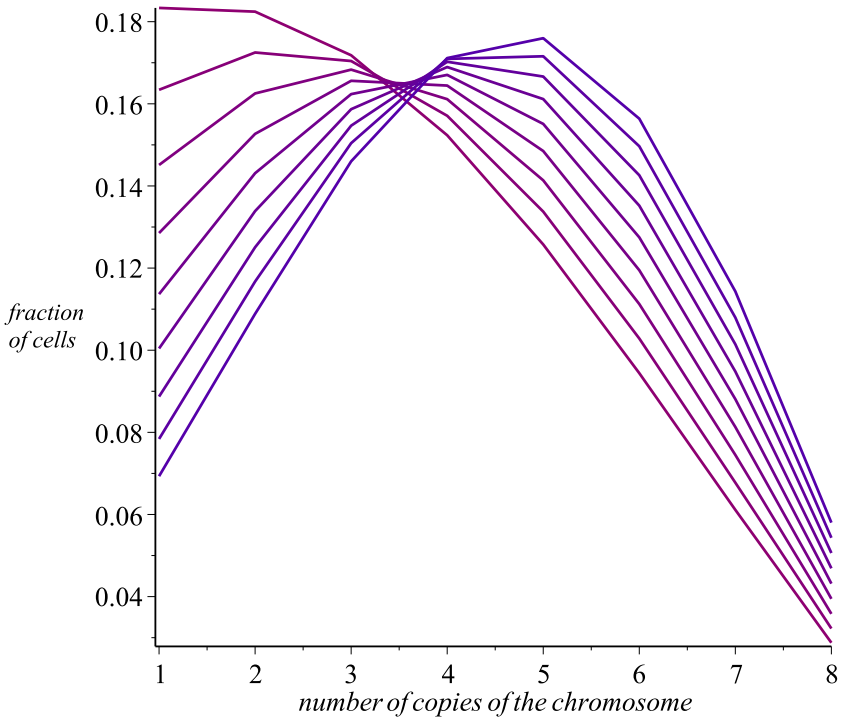
$p = 0.0025$



$p = 0.01$

The limiting distribution

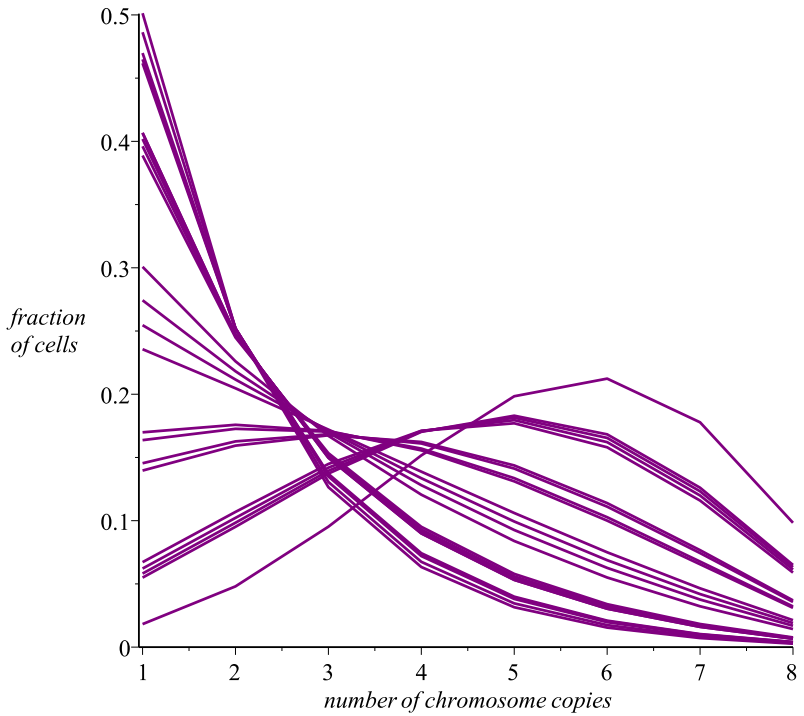
Liming distributions for μ in the refined range 1.0002, 1.00025, 1.0003, 1.00035, 1.0004, 1.00045, 1.005, 1.0055, 1.0006.



$p = 0.0025$

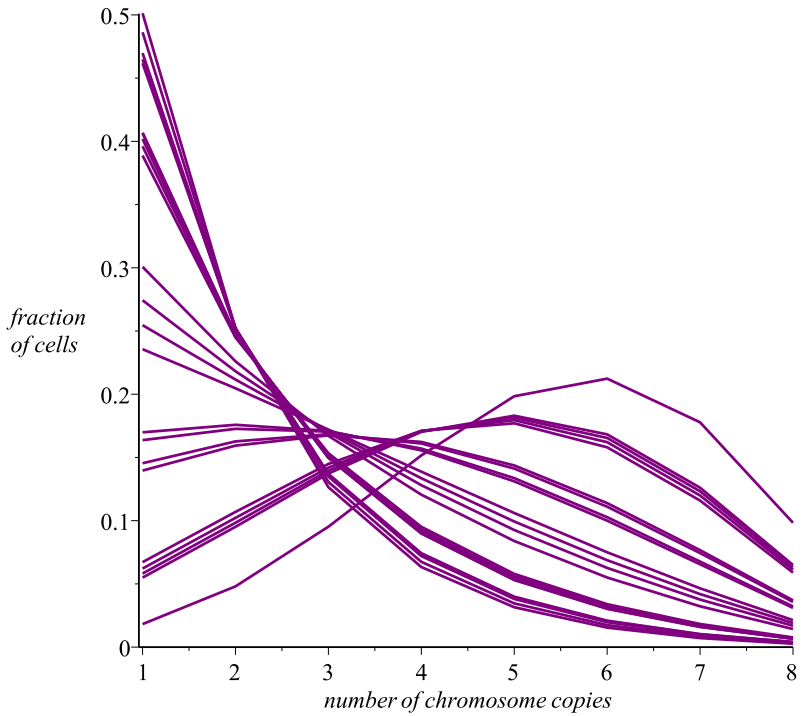
The limiting distribution

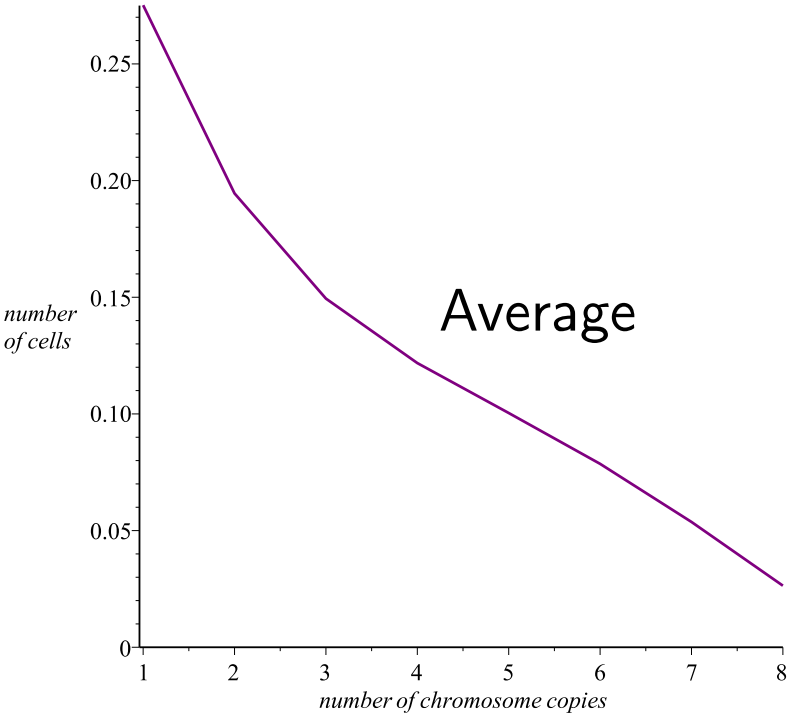
Limiting distributions for the experimentally found values of μ corresponding to the 23 human chromosomes, and $p = 0.0025$:



The limiting distribution

Limiting distributions for the experimentally found values of μ corresponding to the 23 human chromosomes, and $p = 0.0025$:



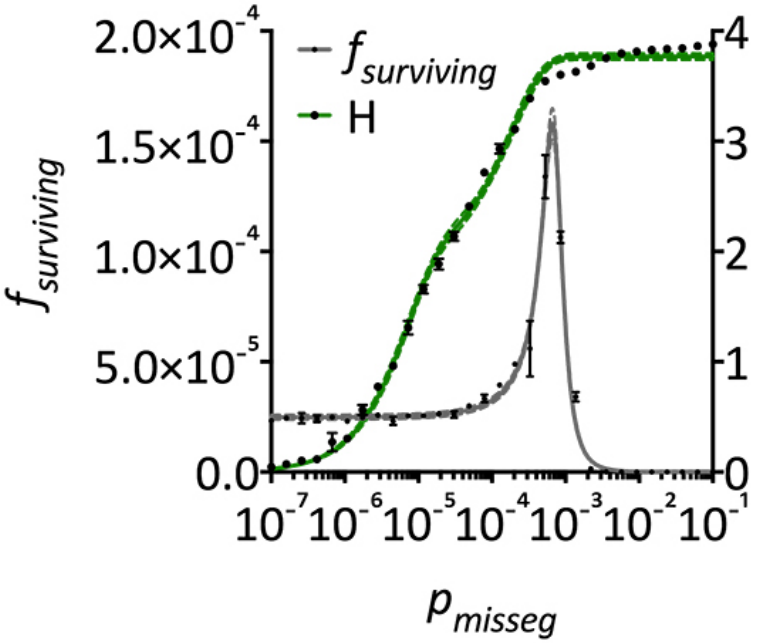


The average number of chromosomes per cell in the limit is 72.7, which is an average of 3.16 copies of each chromosome type.

Fraction of alive cells after 1000 generations

Using the experimentally found values for the chromosome scores and starting with a tetraploid founder cell.

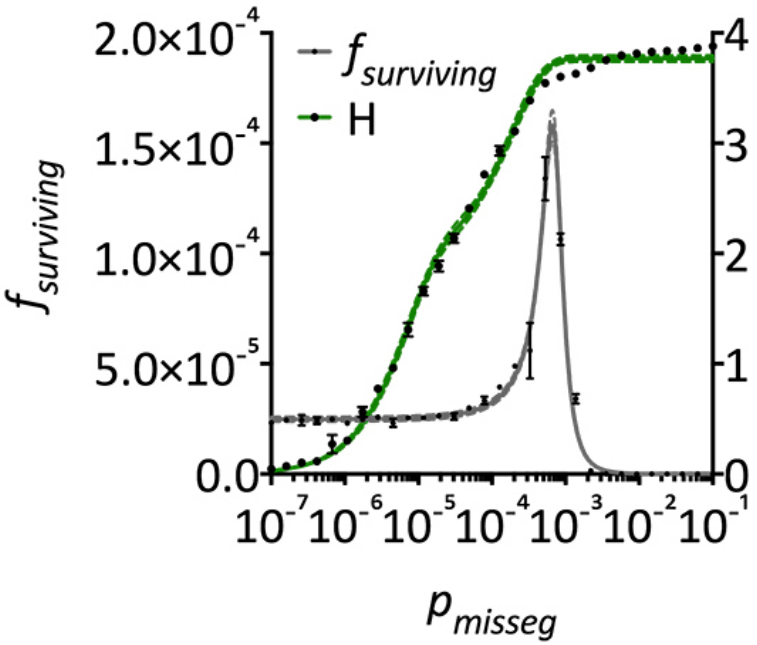
Forward Matlab simulation:



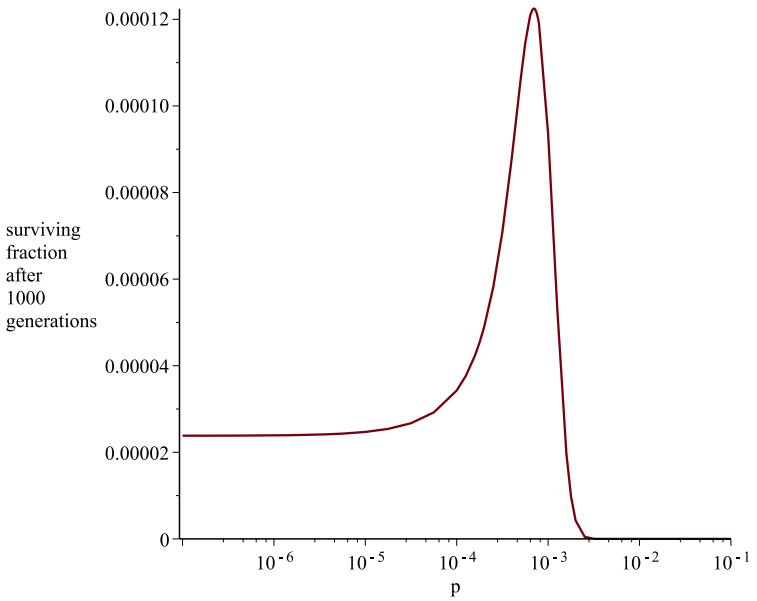
Fraction of alive cells after 1000 generations

Using the experimentally found values for the chromosome scores and starting with a tetraploid founder cell.

Forward Matlab simulation:



Markov chain model:



The number of alive cells is maximized for a narrow range of the missegregation rate, around $p \approx 10^{-3}$.

Changing the survival probability

We can change the survival probability Q_{surv} by multiplying it by a factor F. This is useful to model:

- when the tumor outgrows its blood supply;
- adding treatments to tumors (this makes the survival probability lower only for certain cells).

Changing the survival probability

We can change the survival probability Q_{surv} by multiplying it by a factor F. This is useful to model:

- when the tumor outgrows its blood supply;
- adding treatments to tumors (this makes the survival probability lower only for certain cells).

If we multiply Q_{surv} by F for all cells in our current model with $p = 0.0025$, the size of the tumor increases if $F > 0.51$ and it decreases if $F < 0.50$.

Targeted therapy and mutations

Targeted therapy targets genes located in a particular chromosome, decreasing the survival probability.

Targeted therapy and mutations

Targeted therapy targets genes located in a particular chromosome, decreasing the survival probability.

However, at a given rate $m \approx 10^{-9}$ each target gene is mutated, becoming no longer responsive to treatment. Mutated genes are inherited.

Targeted therapy and mutations

Targeted therapy targets genes located in a particular chromosome, decreasing the survival probability.

However, at a given rate $m \approx 10^{-9}$ each target gene is mutated, becoming no longer responsive to treatment. Mutated genes are inherited.

The survival probability of the cell depends on the number of mutated and normal copies of the treated chromosome.

Modeling mutations

We modify the Markov chain as follows:

States are indexed by pairs (i_1, i_2) with $1 \leq i_1 + i_2 \leq N$, representing cells having i_1 normal copies of the chromosome and i_2 mutated copies. E.g., for $N = 8$, there are 44 non-absorbing states.

Modeling mutations

We modify the Markov chain as follows:

States are indexed by pairs (i_1, i_2) with $1 \leq i_1 + i_2 \leq N$, representing cells having i_1 normal copies of the chromosome and i_2 mutated copies. E.g., for $N = 8$, there are 44 non-absorbing states.

In a cell division, each normal copy of the chromosome has probability $m \approx 10^{-9}$ of mutating (and becoming resistant). Each mutated copy has probability $r \approx 10^{-9}/4$ of reversing into a normal copy (amenable to treatment).

Modeling mutations

We modify the Markov chain as follows:

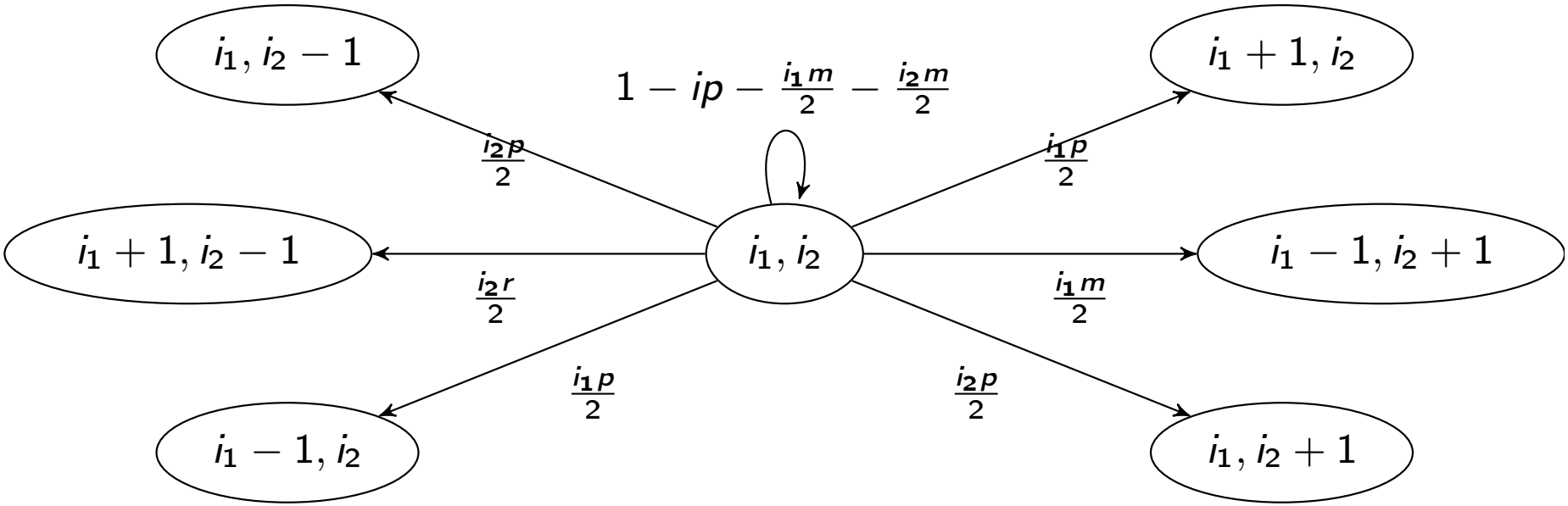
States are indexed by pairs (i_1, i_2) with $1 \leq i_1 + i_2 \leq N$, representing cells having i_1 normal copies of the chromosome and i_2 mutated copies. E.g., for $N = 8$, there are 44 non-absorbing states.

In a cell division, each normal copy of the chromosome has probability $m \approx 10^{-9}$ of mutating (and becoming resistant). Each mutated copy has probability $r \approx 10^{-9}/4$ of reversing into a normal copy (amenable to treatment).

Again, we disregard highly unlikely events such as mutating and missegregating in the same cell division.

The modified Markov chain

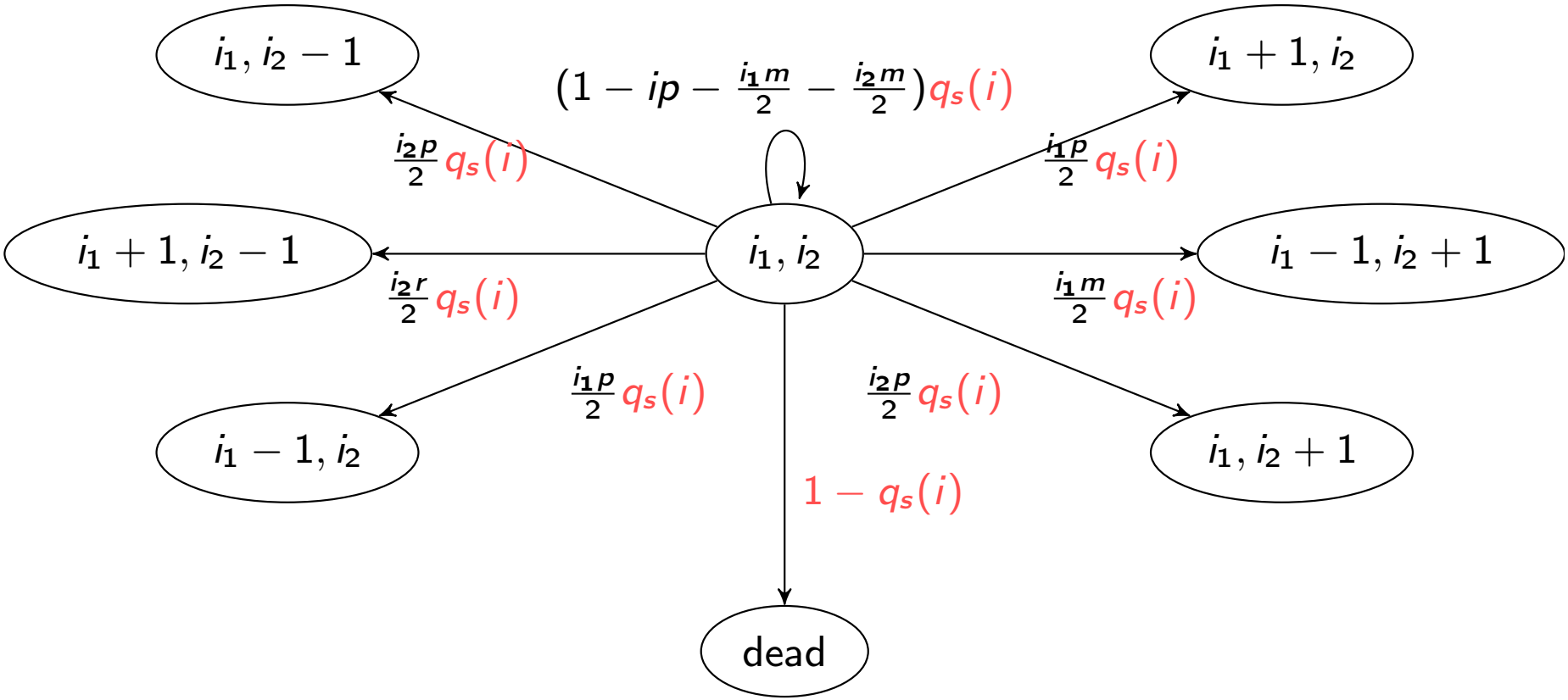
Arrows leaving a typical node (i_1, i_2): (let $i = i_1 + i_2$)



Missegregations and mutations

The modified Markov chain

Arrows leaving a typical node (i_1, i_2): (let $i = i_1 + i_2$)



Missegregations and mutations, survival probability

Modeling drug resistance

First, we let the tumor grow with the usual parameters $(p, Q_{\text{surv}}, m, r)$, until it reaches 10^9 cells and it becomes detectable with a CT scan.

Then we apply a drug that targets a given chromosome.

Modeling drug resistance

First, we let the tumor grow with the usual parameters $(p, Q_{\text{surv}}, m, r)$, until it reaches 10^9 cells and it becomes detectable with a CT scan.

Then we apply a drug that targets a given chromosome.

This can be modeled in two ways:

1. Binary resistance: cells with at least one mutated copy of the treated chromosome are resistant.
2. The level of resistance depends on the ratio of copies of normal vs. mutated target genes.

Case 1: Binary resistance

For cells of type $(i_1, 0)$, multiply the survival probability by a factor F, which depends on the strength of the treatment.

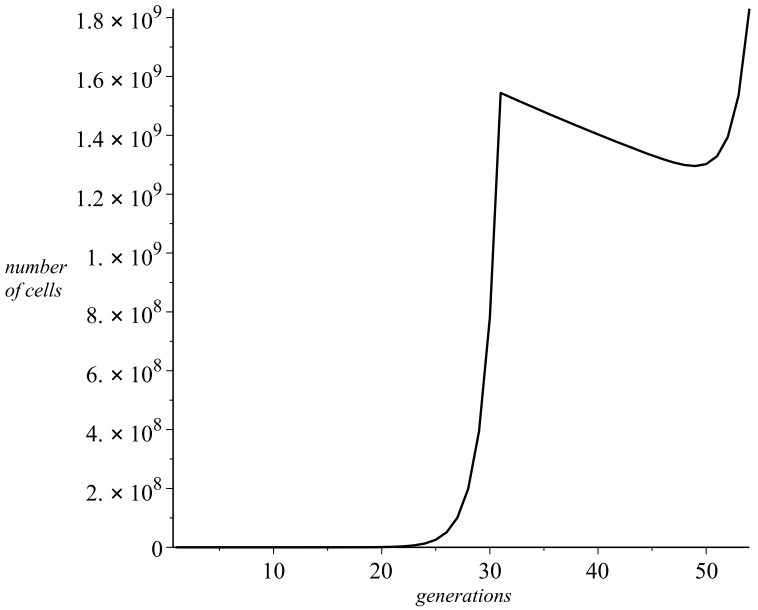
Cells of type (i_1, i_2) with $i_2 > 0$ behave like before.

Case 1: Binary resistance

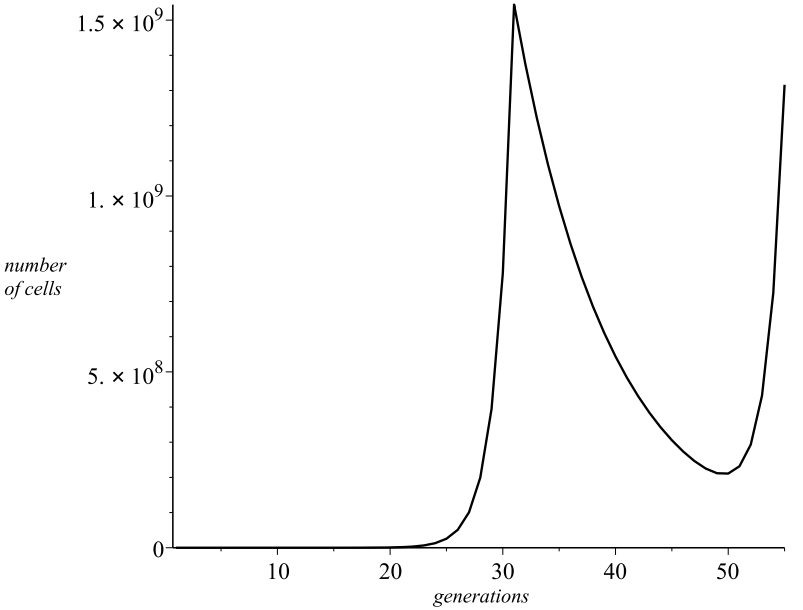
For cells of type $(i_1, 0)$, multiply the survival probability by a factor F, which depends on the strength of the treatment.

Cells of type (i_1, i_2) with $i_2 > 0$ behave like before.

Treatment applied to chromosome 1, tetraploid founder cell:



$F = 0.50$



$F = 0.45$

Case 2: Graded resistance

For cells of type (i_1, i_2), multiply the survival probability by

$$\frac{i_1 F + i_2}{i_1 + i_2}.$$

This factor is F for cells of type $(i_1, 0)$ and 1 for cells of type $(0, i_2)$.

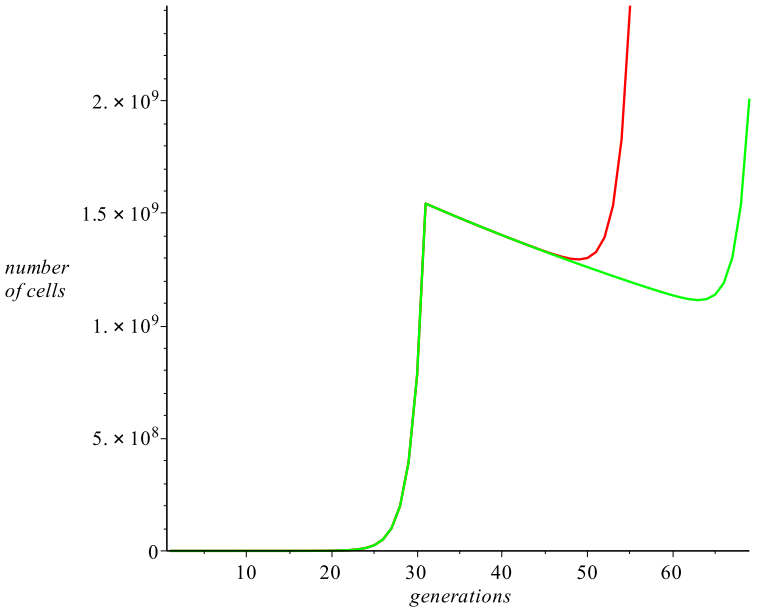
Case 2: Graded resistance

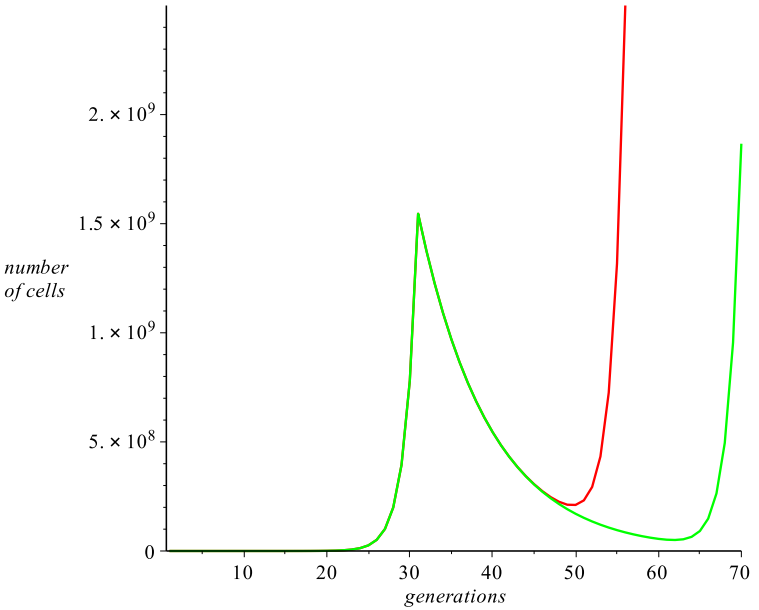
For cells of type (i_1, i_2), multiply the survival probability by

$$\frac{i_1 F + i_2}{i_1 + i_2}.$$

This factor is F for cells of type $(i_1, 0)$ and 1 for cells of type $(0, i_2)$.

Compare binary resistance and graded resistance:





Thank you